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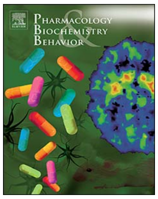

Review

Role of the lateral habenula in memory through online processing of information

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ABSTRACT

Our memory abilities, whether they involve short-term working memory or long-term episodic or procedural memories, are essential for our well-being, our capacity to adapt to constraints of our environment and survival. Therefore, several key brain regions and neurotransmitter systems are engaged in the processing of sensory information to either maintain such information in working memory so that it will quickly be used, and/or participate in the elaboration and storage of enduring traces useful for longer periods of time. Animal research has recently attracted attention on the lateral habenula which, as shown in rodents and non-human primates, seems to process information stemming in the main regions involved in memory processing, e.g., the medial prefrontal cortex, the hippocampus, the amygdala, the septal region, the basal ganglia, and participates in the control of key memory-related neurotransmitters systems, i.e., dopamine, serotonin, acetylcholine. Recently, the lateral habenula has been involved in working and spatial reference memories, in rodents, likely by participating in online processing of contextual information. In addition, several behavioral studies strongly suggest that it is also involved in the processing of the emotional valance of incoming information in order to adapt to particularly stressful situations. Therefore, the lateral habenula appears like a key region at the interface between cognition and emotion to participate in the selection of appropriate behaviors.

1. Introduction

An important question raised in the field of cognitive neuroscience is how life experiences are integrated and memorized to further participate to the building of one's personality, behavioral skills and adaptive behaviors. This is particularly relevant as our cognitive skills, and in particular memory, are fundamental in our every-day life to trigger what is called "memory-based behaviors", which allow us to avoid repeating mistakes and guide our choices.

Memory is multifaceted and comprises short-term memory, including working memory, and long-term memory, including declarative and non-declarative memories (Squire and Dede, 2015). Thus, human and rodent studies have finally concluded that memory is a complex cognitive function requiring diverse brain areas depending of the type of information stored in memory (Ben-Yakov et al., 2015; Frankland and Bontempi, 2005; Henke, 2010; Zola-Morgan and Squire, 1993). Also, it is now well described that besides their nature, the brain structures involved in the storage of our memories depend on their age, leading to different theory of consolidation (Frankland and Bontempi, 2005; Josselyn et al., 2015; Nadel et al., 2012; Winocur et al., 2010). Nevertheless, the entire brain network involved in memory processes remain to be discovered as well as how all these areas may interact in order to trigger, at the end, the most appropriated behavior. Recently, different studies have suggested that the lateral habenula (LHb) may take part in memory processes and perhaps play an important role in the selection of the most adapted "memory-based behavior".

Although the aim of this review is not to exhaustively describe memory at the functional and anatomical levels, we will briefly introduce the principal forms of memory; we will focus on two types of memory processes, a form of short-term memory, namely working memory, and long term memory, and how they are studied in rodents, to latter depict recent findings concerning the involvement of the LHb in those specific forms of memory. We will also briefly describe the main cerebral structures involved in those forms of memory, which are particularly associated with the LHb, in order to, at the end of the review, suggest which brain memory networks the LHb could belong to.

1.1. Working memory

Working memory (WM) refers to our capacity to maintain, during a

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brief delay, manipulate and further use an information before it is disregarded because of no further use (Baddeley, 2012). Preclinical models of WM include tasks addressing the capacity of rodents to maintain an information during several seconds to minutes to further use it in order to choose the correct option among several; those include for example delayed – or non-delayed – matching to position paradigms tested in mazes or operant chambers (Castner et al., 2004; Dudchenko, 2004).

1.2. Long-term memory

The genesis of long-term memory (LTM) requires at least two important steps (Josselyn et al., 2015). The different information composing a particular event are first encoded (Dragoi and Tonegawa, 2013a, 2013b) and then follow consolidation processes in order to be stabilized into specific brain networks (Frankland and Bontempi, 2005; Josselyn et al., 2015; Winocur et al., 2010). The resulting memory may further be recalled, either consciously, in the case of semantic or episodic declarative memories, or unconsciously in the case of implicit memories in a given situation (Squire and Dede, 2015).

In the present review we will focus on rodent models of human long-term episodic-like memory; such a form of memory is studied by means of spatial reference memory tasks, using for example the water maze or the 8-arm radial maze, tasks involving the displacement of objects in known environments, or tasks of emotional memory, using the classical fear conditioning or avoidance tests (Binder et al., 2015; Izquierdo et al., 2016; Morris, 1984). Here we will describe findings regarding the involvement of the LHb in long-term memory using the water maze. Such a task is of particular interest as it allows to analyze different types of swim pattern, or search strategies, that can give an idea about how rats solve this particular situation by choosing the appropriate memory-based strategy.

1.3. Neuroanatomy and neurochemistry of learning and memory

The use in rodents of the above-described tasks has led to the discovery of key brain regions involved in memory processing, bearing a high degree of similarity with the human neuroanatomy; those include the medial prefrontal cortex (mPFC; Frankland et al., 2004; Kesner and Churchwell, 2011; Winocur et al., 2010), the hippocampus (HPC), particularly involved when the behavioral paradigms require navigation and retrieval of places or objects in open spaces (Moser et al., 2015), basal ganglia regions including the mediodorsal striatum (Packard and Knowlton, 2002; Yin and Knowlton, 2006), the amygdala, particularly associated with long-term emotional memory (Gründemann and Lüthi, 2015), various thalamic nuclei (e.g., anterior, lateral) (Wolff et al., 2015), or the septal region (Boyce and Adamantidis, 2017; Boyce et al., 2016). On a pharmacological point of view, in rodents several key neurotransmitter systems modulate learning and memory. For example, dopamine within the mPFC plays a key role in working memory (Floresco, 2013; Puig et al., 2014). According to long term memories, including spatial reference and emotional memories, they involve an action of dopamine and serotonin at the level of the hippocampus and the amygdala (Lisman and Grace, 2005; Pezze and Feldon, 2004; Rossato et al., 2009; Bocchio et al., 2016; Meneses, 2015). Finally, spatial LTM specifically involves the cholinergic projection from the septal area to the HPC (Micheau and Marighetto, 2011).

1.4. From memory to memory-systems

It is interesting to consider the different types of memory with regard to the constant behavioral adaptations to the constraint of their environment individuals are subjected to. Memories are necessary to make decisions and drive our behaviors in order to reinforce or suppress certain actions to, finally, promote adaptive behaviors. We constantly need to integrate all features of an ongoing situation and confront them to our past experiences to promote a behavior or suppress it (McDonald and Hong, 2013; McDonald et al., 2004a). In relation with this point of view, McDonald and colleagues already described in animal models five memory systems based on the behavior triggered by the animals during specific tasks (McDonald et al., 2004b). The authors propose the existence of a HPC-based memory system involved in the elaboration of spatial strategies, whereas a striatum-based system promotes stimulus-response behaviors and participates in habits learning. In addition, a cerebellar and a perirhinal cortical memory system lead, respectively, to classical conditioning of association involving skeletal responses, and complex visual object memory processes. Finally, one last system would involve the amygdala and participate in emotional memory. The existence of these different memory systems, involving distinct brain networks, will further allow the use of different behavioral strategies depending on the ongoing situation.

2. Involvement of the lateral habenula in memory processes

2.1. Anatomical and pharmacological aspects

It is interesting to notice that the LHb, such as shown in cats, rodents and monkeys, is connected, either directly or indirectly, with the main above-described networks involved in memory processes. The LHb receives direct projections from the mPFC (Chiba et al., 2001; Kim and Lee, 2012; Vertes, 2006), the medial septal area (Meibach and Siegel, 1977), and is directly or indirectly connected with the entire basal ganglia (Hong and Hikosaka, 2013). While inputs from the basal ganglia, and more precisely from the monkey's internal portion of the globus pallidus (the rodents' entopeduncular nucleus), are more particularly involved in the signalling of error-prediction (Hikosaka, 2010; Matsumoto and Hikosaka, 2007, 2009), Bromberg-Martin and Hikosaka (2011) further proposed that the information transmitted by the basal ganglia to the LHb serves the latter to participate in the evaluation of the immediate consequences of an action and to anticipate the occurrence of a reward or a punishment; this appears particularly interesting because it positions the LHb as a link between our past experiences (memories) and the ongoing situation. The LHb is indirectly connected with the dorsal HPC (dHPC) in rats, as Goutagny et al. (2013) and Aizawa et al. (2013) found coherent activity at theta frequency between both structures, suggesting the likelihood of an exchange of information (Fries, 2005, 2015), including regarding spatial memory processes (Goutagny et al., 2013). Also, Mok and Mogenson (1974) recorded in anesthetized rats cellular responses within the LHb while they stimulated various telencephalic structures. They observed that 55% of the recorded LHb neurons responded to stimulation of the dHPC, while 66% of the recorded LHb neurons responded to stimulation of several nuclei of the amygdala; interestingly, 51% of the recorded LHb neurons responded to both hippocampal and amygdalar stimulation, further suggesting that the LHb represents a recipient of information coming from the whole temporal lobe, which is crucially involved in short- and long-term memory processes. Finally, the LHb projects to the mediodorsal nucleus of the thalamus (Araki et al., 1988), particularly involved in memory processes (Wolff et al., 2015). Altogether, these studies help suggesting that the LHb is in good position to process memory as it is connected with the main networks mediating such a function.

Moreover, the LHb has been shown to interact with the key neurotransmitter systems involved in memory processes. It participates to the modulation of the activity of midbrain dopamine neurons, and of dopamine release in the mPFC and the basal ganglia (Brown and Shepard, 2016; Lecourtier et al., 2008); it modulates the activity of raphe serotonergic neurons (Wang and Aghajanian, 1977), as well as serotonin transmission (Kalén et al., 1990). Montalbano et al. (1991) and Zagami et al. (1995) further proposed that the LHb influences hippocampal cellular activity through an action on the raphe. Finally,